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Applicant:	Olli Vuolteenaho et al.	Confirmation No.:	9413
Serial No.:	10/562,081	Art Unit:	1647
Filed:	April 5, 2006	Examiner:	Shulamith H. Shafer
Customer No.:	21559		
Title:	Methods of Determination of Activation or Inactivation of Atrial Natriuretic Peptide (ANP) and Brain Natriuretic Peptide (BNP) Hormonal Systems		

PRE-APPEAL BRIEF REQUEST FOR REVIEW

Applicants request review of the final rejection dated July 9, 2010 in connection with the above-captioned application. No amendments are being filed with this request. This request is being filed with a Notice of Appeal. The review is requested for the reasons stated on the following page. If there are any charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

Date: November 3, 2010

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REMARKS

Claims 1-4, 7-10, 12-17, 29-37, 40-44, and 62-68 are pending in the application. Claims 29-37 and 40-44 were withdrawn from consideration, pursuant to a Restriction Requirement. Claims 1-4, 7-10, 12-17, and 62-68 were rejected. The rejections are addressed below.

As an initial matter, Applicants again note that the central feature of the claimed invention is determination of activation of ANP and BNP without measuring the individual levels of proANP and proBNP. This is based on the discovery that, in contrast to the prior art diagnostic methods, which were based on the desirability of determining the levels of proANP and proBNP individually, detection of the combined levels of proANP and proBNP provide useful diagnostic information. Claim 1 captures this discovery by reciting that the detection of proANP and proBNP occur "in a single reading, in a single assay" and by specifying that the claimed method "does not comprise detection of the presence of proANP and proBNP or fragments thereof individually."

Rejections under 35 U.S.C. § 112, first paragraph, enablement and written description

In an advisory action dated October 6, 2010, the Office withdrew the rejections for insufficient written description and lack of enablement.

Rejection under 35 U.S.C. § 112, second paragraph

Claims 3, 4, and 9 remain rejected for failure to include essential steps. The Office states "[a]bsent any recitation that the fusion polypeptide or peptide is labeled in some way that would distinguish the calibration agent or competitive inhibitor from the proANP or proBNP that is present in the sample to be tested, one would not be able to distinguish between the presence or amount of atrial and brain natriuretic peptide prohormones that are present in the sample as a result of activation or inactivation of the hormonal system as recited in claim 1." (Advisory Action, pg. 2, ¶ 6). As Applicants have previously submitted, a recitation of a functional limitation for the claimed fusion polypeptide should be considered to be sufficient to render the claim term definite.[1] (Reply filed September 7, 2010 (herein "the Reply"), pg. 13, ¶ 2).

[1] "A functional limitation is an attempt to define something by what it does, rather than by what it is (e.g., as evidenced by its specific structure or specific ingredients). There is nothing inherently wrong with defining some part of an invention in functional terms. Functional language does not, in and of itself, render a claim improper. *In re Swinehart*, 439 F.2d 210, 169 USPQ 226 (CCPA 1971).

One skilled in the art at the time of the invention would have understood the nature and role of a "calibration agent" and a "competitive inhibitor" without recitation of a particular structural feature (e.g., a detectable label). Furthermore, one skilled in the art at the time of the invention would have been able to readily conceive of embodiments of the claimed invention that included, e.g., unlabelled calibration agents (e.g., where the fusion polypeptide is introduced at a known concentration, thereby rendering separate quantification of the calibration agent unnecessary). Therefore, the claimed "capability or purpose" of the fusion polypeptide is "fairly [conveyed] to a person of ordinary skill in the pertinent art in the context in which it is used." The rejection of claims 3, 4, and 9 for omitting essential steps should be withdrawn. (Id., at ¶ bridging pgs. 13 and 14).

Rejections under 35 U.S.C. § 103(a)

Claims 1, 16, 17, 62-66, and 68 were rejected under 35 U.S.C. § 103(a) for obviousness over Clerico et al., J. Endoc. Invest. 21:170-179, 1998, in view of Clerico et al., Clin. Chemistry 46:1529-1534, 2000. Applicants request that this rejection be reconsidered and withdrawn.

The Office argues that, contrary to the discovery on which the currently claimed invention is based, the phrase "single reading, in a single assay" encompasses the simultaneous separate measurement of proANP and proBNP in the same sample volume. Furthermore, the Office states:

> It is noted that Claim 1, one of the independent claims of the instant invention has been amended to recite "wherein said method does not comprise detection of the presence of proANP and proBNP or fragments thereof individually." It is the Examiner's position that this amendment to the claim reinforces the preamble to the claim and does not remove the ideas that flow naturally from the teachings of the prior art, that the detection of proANP and proBNP may be performed in a single assay in a single reading. (Final Office Action, pg. 25, ¶ 2).

Based on this interpretation of claim 1, the Office states that

> one of ordinary skill, aware that it is routine to detect multiple compounds in a single sample at the same time in the performance of clinical assays (for example, a lipid profile, liver enzyme assays), would be motivated to assay both ANP and

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A functional limitation must be evaluated and considered, just like any other limitation of the claim, for what it fairly conveys to a person of ordinary skill in the pertinent art in the context in which it is used. A functional limitation is often used in association with an element, ingredient, or step of a process to define a particular capability or purpose that is served by the recited element, ingredient or step." (M.P.E.P. § 2173.05(g); Emphasis added).

> BNP in the same assay to increase the efficiency and reduce the costs of said assays. Techniques utilizing immunoassays for simultaneous detection of two polypeptides in a single reading in a single assay were well known at the time of the instant invention, as evidenced by Swartzman et al which teaches simultaneous detection of two cytokines, IL-6 and Il-8 in the same high-throughput multiplexed immune assay. (Citations omitted). (Advisory Action, ¶ bridging pgs. 2 and 3).

By suggesting that Swartzman is relevant to the claimed invention, the Office appears to conflate the claim term "a single reading" with the claim term "a single assay." While Swartzman does describe an assay for measuring IL-6 and IL-8 simultaneously in a single assay, each cytokine produces a separate reading (see, e.g., figure 4A, which shows the average fluorescent intensity corresponding to IL-6 in grey bars and IL-8 in white bars). (The Reply, pg. 16, ¶ 3).

Furthermore, Applicants respectfully request that the Office again consider the limitation that the claimed method does not include detection of the proteins "individually." M.P.E.P. § 2143.03 states "'[a]ll words in a claim must be considered in judging the patentability of that claim against the prior art.' *In re Wilson*, 424 F.2d 1382, 1385, 165 USPQ 494, 496 (CCPA 1970)." With regard to negative limitations, the M.P.E.P. § 2173.05(i) states "[t]he current view of the courts is that there is nothing inherently ambiguous or uncertain about a negative limitation. So long as the boundaries of the patent protection sought are set forth definitely, albeit negatively, the claim complies with the requirements of 35 U.S.C. 112, second paragraph." The Office does not cite a publication teaching the claim limitation that proANP and proBNP, or fragments thereof, not be measured individually, because Swartzman, Clerico (1999), and Clerico (2000) all describe the individual measurement of separate analytes (e.g., ANP and BNP). Particularly in view of the claim limitation that the proteins be detected in a single reading and not individually, Applicants respectfully submit the invention of claim 1 would not have been obvious over the cited art. (The Reply, pg. 16, ¶ 4).

The Office also states that the teachings of the two Clerico references are compatible with the claimed invention, as both Clerico references teach that "ANP and BNP are greatly elevated in patients with clinical severe disease, such as severe heart failure." (Final Office Action, ¶ bridging pgs. 28 and 29). The Office concludes that "elevated levels of BNP, ANP or both would be diagnostic of heart failure, as recited in claim 17 of the instant invention" (Id.) and that "one of skill in the art would anticipate success in detecting both proteins simultaneously." (Id.,

at pg. 28, ¶ 3). Furthermore, the Office argues that "[o]ne of ordinary skill, aware of the teachings of the cited references, and in the interests of efficiency could easily design such an assay: for example by labeling an antibody to pro-ANP and an antibody to pro-BNP . . . with the same detectable label." (Advisory Action, pg. 3, ¶ 6).

Notwithstanding these observations, neither Clerico reference teaches that it would have been useful to measure both proANP and proBNP, or fragments thereof, without distinguishing between the two proteins. The Office disregards the teachings of both Clerico references that indicate the desirability of separate measurement of individual ANP and BNP for the purpose of efficiency. When considered as a whole, Clerico (1998) provides a rationale for measuring ANP and BNP *separately* as "the data reported in Figure 3 suggest that the BNP assay is more useful than the ANP assay for discriminating between normal subjects and patients with cardiomyopathy, even including those with only mild symptoms" (page 176, column 1). Furthermore, as stated by the Office, Clerico (2000) teaches

> [i]n some studies, the assay for N-terminal proANP1-98 peptides (the elected species of the instant invention) was shown to be equally or even more clinically useful than other CNH assays, whereas in others BNP was found to be the best marker of myocardial involvement.

Based on these statements, Clerico (1998) and Clerico (2000) teach the desirability of distinguishing between ANP and BNP levels and, therefore, teach away from the claimed methods, which require a single reading, in a single assay, for detecting the presence of proANP and proBNP, or fragments thereof, without distinguishing between the two polypeptides.

The Office's statement that one skilled in the art would anticipate success in performing Applicants' assay does not provide an objective reason based on the Clerico references to measure proANP and proBNP, or fragments thereof, in a single reading, in a single assay, as required for a finding of obviousness. (The Reply, pg 17, ¶¶ 1-4).

The Office did not provide an "objective reason" why one skilled in the art at the time of the invention would have modified the teachings of the Clerico references to measure ANP and BNP levels without detecting the proteins individually.[2] Consequently, the Office's selective

[2] M.P.E.P. § 2143.01(IV) states "A statement that modifications of the prior art to meet the claimed invention would have been 'well within the ordinary skill of the art at the time the claimed invention was made' because the references relied upon teach that all aspects of the claimed invention were individually known in the art is not sufficient to establish a *prima facie* case of obviousness without some objective reason to combine the teachings of the references. *Ex parte Levengood*, 28 USPQ2d 1300 (Bd. Pat. App. & Inter. 1993; emphasis original)."

reading of the Clerico references to support a *prima facie* case of obviousness appears to be based on the hindsight afforded by Applicants' own disclosure. Nowhere do any of the cited references teach or suggest the measurement of proANP and proBNP, or fragments thereof, in a single reading, in single assay, without detection of two proteins individually. Therefore, the rejection for obviousness should be withdrawn. (Id., at ¶ bridging pgs. 17 and 18).

Claims 2-4, 7-10, 12-15, and 67 were rejected for obviousness over Clerico (1998), in view of Clerico (2000), and further in view of Buechler et al., U.S. Patent No. 7,341,838.

The Clerico references were cited for the reasons discussed above. Buechler ('838) was cited for describing amino acid sequences bearing similarity to SEQ ID NOs:3 and 6, which are stated by Buechler ('838) to correspond to proANP and proBNP. The Office states that those of skill in the art would have recognized that antibodies that recognize the sequences of Buechler ('838) would also recognize the sequences of the present claims, and that Buechler ('838) teaches measuring the amounts of ANP and BNP-related fragments by using antibodies, including bivalent antibodies. In view of these teachings, the Office concludes that it would have been obvious to modify the methods of Clerico (1998 and 2000) by substituting the sequences taught by Buechler ('838) and utilizing bispecific antibodies, as taught by Buechler ('838). Applicants respectfully disagree and request that this rejection be reconsidered and withdrawn.

As discussed above, a central feature of the present invention is the detection of the presence of both proANP and proBNP-related sequences in a single reading, in a single assay. Also as discussed above, it would not have been obvious in view of either Clerico reference to perform a single assay to obtain a single reading that determines the presence of proANP and proBNP, or fragments thereof, without distinguishing between the two polypeptides. Buechler ('838) does not add what is missing from the Clerico references in supporting this rejection, as Buechler ('838) does not teach or suggest testing for the presence of proANP and proBNP-related sequences in a single reading, in a single assay. In view of the above, Applicants request that this rejection be reconsidered and withdrawn. (Id., at pg. 18, ¶¶ 2 and 3).